**News and Views**

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**Weight loss is the major player in bariatric surgery benefits**

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**Competing interests**

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**Headline Summary**

*A metabolic study comparing people who lost weight through dieting or bariatric surgery shows that the effects are due to weight loss.*

Type 2 diabetes is an important complication of obesity that can lead to significant health complications, including blindness, kidney failure, amputations and cardiovascular disease resulting in adverse effects on quality of life and life expectancy. It is a progressive disease, with obesity inducing insulin resistance which is compensated for by a progressive increase in insulin secretion from the pancreatic β-cells eventually leading to β-cell failure. There is no question that weight loss is an effective treatment, especially in the early stages of the disease, before pancreatic β-cell failure becomes established and that this is due to improvements in insulin sensitivity in the liver, adipose tissue and muscle as well as recovery of β-cell function1.Bariatric surgery, especially Roux-en-Y gastric bypass (RYGB) has also been shown to be an effective therapy for type 2 diabetes, however it was unclear whether the effects of this surgery are independent of weight loss. A recent study in the *New England Journal of Medicine* found that people who had lost weight by dieting had underwent similar changes in their diabetes to those that lost the same amount of weight after RYGB surgery.

One of the first studies to show that diet was able to induce remission of diabetes in a real-world clinical setting isthe DiRECT study, where a low energy diet was able to induce remission of diabetes in over 45% of people who lost an average of 11% of body weight. 2. It is however difficult to maintain weight loss from lifestyle support alone, and bariatric surgery, especially Roux-en-Y gastric bypass (RYGB), a form of weight loss surgery that works by both reducing the size of the stomach and bypassing the duodenum (figure 1) has been shown to be more effective than medical therapy for control of type 2 diabetes in long-term studies3.

Ever since the surgeon Walter Pories reported the rapid effects of RYGB to improve diabetes in the 1990s4, it was suggested that bariatric surgery, particularly RYGB, has effects that improve glucose metabolism beyond weight loss. People who have undergone RYGB have more rapid than normal entry of glucose and other nutrients into the circulation. In addition alterations in gut hormones in individuals who have undergone RYGB, particularly increased secretion of glucagon-like peptide 1 (GLP1), have been suggested to be a potential mechanism by which improved insulin secretion and rapid resolution of diabetes is achieved in the early period after surgery in these individuals5. However, GLP1 does not have clinically meaningful effects on insulin sensitivity and the improvements in glucose metabolism cannot be readily explained by the modest changes that are seen after RYGB. Many other aspects of gut and nutrient physiology are altered after RYGB, including the levels of circulating branch chain amino acids, bile acids and alterations in the gut microbiome, all of which may alter insulin sensitivity (figure 1) but whether these changes can explain the profound improvements in glucose metabolism after surgery remains uncertain6.

Yoshino *et al* set out to answer whether the improvements in glucose metabolism in people with diabetes who have undergone RYGB due to weight loss alone. Their study compared 11 people with type 2 diabetes who had lost 16-18kg by following a strict energy restricted diet, with 11 who had lost a similar amount of weight about 16 weeks after a RYGB7. They carried out detailed measurements of glucose metabolism in these people using a glucose clamp approach that allowed assessment of multiorgan insulin sensitivity (liver, muscle and adipose tissue) before and after weight loss. They also assessed insulin secretion in these individuals from a combination of the clamp data and the individuals’ responses to a standardised test meal to allow assessment of their β-cell function. The authors also studied the metabolic effects of standardised liquid meals over a 24-hour period on these individuals, as well as measuring circulating branched chain amino acids, bile salts and the profile of the gut microbiome in the same group. Both groups were similar in age (49 years) and had diabetes for about 10 years at the time of the interventions. They were on a variety of glucose lowering medication prior to surgery or starting the diet, which was reduced by about 75% following weight loss in both groups and all medication, except insulin if needed, was stopped three days before the tests, so it is unlikely that possible differences between the groups were due to differences in background diabetes treatment.

The authors found that there were no meaningful differences in multiorgan insulin sensitivity or β-cell function between the groups, and that the improvements in glucose metabolism occurred as a result of weight loss, rather than any weight loss independent effects of surgery in those that underwent RYGB. However, the authors did find that there were meaningful differences in the individuals’ responses to the meal tolerance test. Those who had undergone surgery show a much more rapid rises in circulating glucose, free fatty acids and insulinin response to a meal after surgery compared to those who had undergone dietary weight loss; in particular the peak glucose one hour after the meal was higher than normal.

GLP1 is an important incretin hormone which contributes to the normal stimulation of insulin after a meal, and also signals satiety to the brain. Although measurement of GLP1 levels was included in the authors’ protocol, these data have not been provided in the data published so far – it would be interesting and relevant to have this information to help interpret the observed changes in insulin secretion during the test meal and 24-hour profiles. Furthermore, levels of circulating branched chain amino acids after the test meals were lower after weight loss in both groups, but much lower in those who had surgery. Also, in this group, bile acids were higher and there were marked differences in the microbiome between the individuals that underwent surgery vs. those who lost weight through diet alone after weight loss. These are certainly not normal physiological responses to a meal, and although RYGB is an effective treatment for some people with type 2 diabetes and is associated with improvements in other obesity-related complications, including cardiovascular disease risk8 it is not without potential adverse effects. These are known to be partly a result of the rapid gastric emptying seen after RYGB, including severe hypoglycaemia, often associated with symptoms of dumping syndrome, which can be debilitating for some patients9. RYGB may also cause multiple vitamin deficiencies that remain common in clinical practice despite guidelines advocating lifelong monitoring and replacement10. The move towards sleeve gastrectomy, which reduces the size of the stomach without bypassing the duodenum, as the preferred bariatric procedure may mitigate some of these adverse effects, but only randomised clinical trials, such as the ongoing BYBANDSLEEVE trial in the UK (NCT02841527) will answer the question as to the best bariatric procedure for weight loss and diabetes remission.

Non-specialists might ask why we need bariatric surgery if the effects on diabetes are similar for dietary weight loss. The reality is that losing weight through change in diet alone is really difficult, and most people regain weight because of the physiological responses to weight loss such as increased hunger and slower metabolism11. Surgery is able to overcome these responses partly due to changes in gut hormones, so is still a useful option for people with diabetes who cannot lose weight by other means. The observations made by Yoshino and colleagues remind us that weight loss is an important goal for people with type 2 diabetes, that should improve metabolic control no matter how it is achieved.

**References**

1 Lim, E. L. *et al.* Reversal of type 2 diabetes: normalisation of beta cell function in association with decreased pancreas and liver triacylglycerol. *Diabetologia* **54**, 2506-2514, doi:10.1007/s00125-011-2204-7 (2011).

2 Lean, M. E. J. *et al.* Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. *Lancet* **391**, 541-551, doi:10.1016/s0140-6736(17)33102-1 (2018).

3 Mingrone, G. *et al.* Bariatric-metabolic surgery versus conventional medical treatment in obese patients with type 2 diabetes: 5 year follow-up of an open-label, single-centre, randomised controlled trial. *Lancet* **386**, 964-973 (2015).

4 Pories, W. J. *et al.* Who would have thought it - an operation proves to be the most effective therapy for adult-onset diabetes-mellitus. *Annals Of Surgery* **222**, 339-352 (1995).

5 Korner, J., Bessler, M., Inabnet, W., Taveras, C. & Holst, J. J. Exaggerated glucagon-like peptide-1 and blunted glucose-dependent insulinotropic peptide secretion are associated with Roux-en-Y gastric bypass but not adjustable gastric banding. *Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery* **3**, 597-601, doi:10.1016/j.soard.2007.08.004 (2007).

6 Chondronikola, M., Harris, L. L. S. & Klein, S. Bariatric surgery and type 2 diabetes: are there weight loss-independent therapeutic effects of upper gastrointestinal bypass? *Journal of Internal Medicine* **280**, 476-486, doi:10.1111/joim.12527 (2016).

7 Yoshino, M. *et al.* Effects of Diet versus Gastric Bypass on Metabolic Function in Diabetes. *New England Journal of Medicine* **383**, 721-732, doi:10.1056/NEJMoa2003697 (2020).

8 Sjostrom, L. *et al.* Association of Bariatric Surgery With Long-term Remission of Type 2 Diabetes and With Microvascular and Macrovascular Complications. *Jama-Journal Of The American Medical Association* **311**, 2297-2304, doi:10.1001/jama.2014.5988 (2014).

9 Salehi, M., Vella, A., McLaughlin, T. & Patti, M. E. Hypoglycemia After Gastric Bypass Surgery: Current Concepts and Controversies. *Journal of Clinical Endocrinology & Metabolism* **103**, 2815-2826, doi:10.1210/jc.2018-00528 (2018).

10 O'Kane, M. *et al.* British Obesity and Metabolic Surgery Society Guidelines on perioperative and postoperative biochemical monitoring and micronutrient replacement for patients undergoing bariatric surgery-2020 update. *Obesity Reviews*, doi:10.1111/obr.13087.

11 Sumithran, P. *et al.* Long-Term Persistence of Hormonal Adaptations to Weight Loss. *New England Journal of Medicine* **365**, 1597-1604, doi:10.1056/NEJMoa1105816 (2011).

**Figure 1**

